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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,725	01/13/2000	Ajit Lalvani	GRT/3773-19	6572

23117 7590 04/13/2007

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/308,725	LALVANI ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006 and 23 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed December 20, 2006 and January 23, 2007 are acknowledged and entered. Claims 40-50 remain pending and under examination.

Information Disclosure Statement

2. The DE 195257484 reference was not initialed because the reference itself has not been provided. That the English translation of the search report (that indicates the degree of relevance of the DE 195257484 reference found by the foreign patent office) has been considered, is not the same as considering the document itself. Therefore, the document itself is required if it is to be considered on the PTO Form-1449.

Declaration

3. The application data sheet filed December 20, 2006 is acknowledged and entered. Therefore, there is no requirement for a new oath/declaration.

Specification

4. The objection to the specification for lacking a brief description of the drawings is withdrawn in view of Applicant's amendment filed December 20, 2006.

Claim Rejections - 35 USC § 112

5. The rejection of claim 42 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of Applicant's amendment.

Summary of the claimed invention and claims interpretation

6. The claims are drawn to a method of assay in which peptide-specific effector T-cells are enumerated, which method comprises:

a. providing a fluid containing fresh T cells, which have not been cultured *in vitro*, in contact with a surface carrying an immobilized antibody to interferon-γ (IFN-γ),

b. presenting to the T cells a T cell-activating peptide,

c. incubating the fluid to cause release of said IFN-γ, and

d. detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells;

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by in vitro culture in the presence of the T cell-activating peptide; and said method being applied to diagnosis or monitoring of infection with an intracellular pathogen. Specifically, the intracellular pathogen is selected from the group consisting of hepatitis B (HBV), hepatitis C (HCV), *M. tuberculosis*, *P. falciparum*, human immunodeficiency virus (HIV), and influenza virus. The T cell activating peptide is of 7-12 amino acid residues in length. The peptide is added to the T cell containing fluid, which is

recognized by $CD8^+$ T cells. The peptide is a pre-determined, more specifically, the peptide is the *M. tuberculosis* ESAT-6 peptide. The T cells are peripheral blood mononuclear cells (PBMCs). Particularly, the T cells are taken from a patient known to be suffering, or to have suffered from, infection with an intracellular pathogen. The fluid mixture is incubated under non-sterile conditions. The incubation is continued for a time of 4 to 24 hours.

The claimed assay in intended to monitor progress of HIV infection. The method is also intended to monitor the effect of a vaccine. The Office maintains its position that the subject matter of claims 49-50 is non-limiting because the claims recite, "The method as claimed in claim 40 performed to monitor progress of HIV infection". There is no active monitoring step given the claim language. The Office interprets claims 49-50 as essentially saying, "The method as claimed in claim 40, used for performing the monitoring of progress of HIV infection". Such a limitation does not carry patentable weight, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine.

Claim Rejections - 35 USC § 102

7. The rejection of claims 40, 41, 43 and 46-50 under 35 U.S.C. 102(b) as being clearly anticipated by Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara") is withdrawn. Applicant's arguments have been carefully considered. The rejection is withdrawn because the claim 40 requires that the T cells be presented to a T cell-activating peptide to which the T cells have already been pre-sensitized *in vivo*. In Hagiwara, the T cells used in the ELIspot assay are not expected to be pre-sensitized *in vivo* to PHA mitogen, the T cell-activating peptide to which Hagiwara's T cells are exposed in

the assay. Therefore, the rejection is withdrawn. The only difference between the instant method and Hagiwara's method is that Hagiwara uses PHA mitogen instead of a T cell activating peptide from the pathogen that has infected the cells of the individual being diagnosed/monitored.

8. The rejection of claims 40, 43, 46, 47, 49 and 50 under 35 U.S.C. 102(b) as being clearly anticipated by Klinman *et al.* (*Current Protocols in Immunology*, 1994, 6.19.1-1.19.8, "Klinman"), is withdrawn. Applicant's arguments have been carefully considered. The rejection is withdrawn because Klinman does not specifically teach the use of fresh T cells, as required by the claims. As Applicant notes, the referenced protocols in Klinman suggested the incubation of T cells with a T-cell activating peptide for several days, which involves the culture T cells *in vitro*. The instant claims do not use T cells that have been cultured *in vitro*. The results of incubating for several days with a T cell activating peptide is that memory T cells will be activated in addition to effector T cells. The instant method monitors effector T cells, not memory T cells, by using fresh T cells and incubating the T cells for no more than 24 hours. Therefore, the rejection is withdrawn.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The rejection of claims 40 and 45 under 35 U.S.C. 103(a) as being unpatentable over Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"), is withdrawn for the reasons outlined above.

11. Claims 40-43 and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surcel *et al.* (*Immunology*, 1994, 81:171-176, "Surcel"), in view of Sørensen *et al.* (*Infection and Immunity*, 1995, 63(5):17170-1717, "Sørensen"), is withdrawn. Applicant's arguments have been carefully considered. The rejection is withdrawn because Surcel's measurement of IFN-gamma producing T cells involves incubation of T cells in the presence of a T cell-activating peptide for, what is reasonably deduced from the context of the protocol, 72 hours (page 172, second column, fourth full paragraph). The incubation of T cells with T cell activating peptide for 72 hours would allow memory T cells to proliferate, thus the measurement of IFN-gamma producing T cells would include both the memory T cells and effector T cells. Therefore, the rejection is withdrawn.

12. Claims 40 and 43-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyahara *et al.* (*Journal of Immunological Methods*, 1995, 181:45-54, "Miyahara") in view of Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara"). Previously, claims 45 and 49-50 were not included in this rejection. The claims are summarized above.

Miyahara discloses the quantification of antigen specific $CD8^+$ T cells specific for the epitope SYVPSAEQI of a rodent malaria antigen using an ELIspot assay. The mice were

previously immunized with *Plasmodium yoelii.* Miyahara performed the ELIspot assay with a murine $CD8^+$ T cell clone, YA26, which recognizes a class I MHV restricted epitope (SYVPSAEQI) of the CD protein of *P. yoelii* (page 47, "Results"). After the antigen stimulation, IFN-γ secreted by $CD8^+$ T cells was measured and cells were enumerated. Miyahara does not disclose the use of fresh T cells that have not been cultured *in vitro*.

However, Hagiwara teaches that ELIspot results are divergent when studying PBMC that had been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Miyahara's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo*. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128). The method of assay in which peptide-specific effector T-cells are enumerated, comprises:

a) providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro*, in contact with a 96-well nitrocellulose-backed micro titer plate coated with ant cytokine antibodies ("a surface carrying an immobilized antibody to interferon-γ"),

b) stimulating the cells with a 1:100 dilution of phytohemagglutinin ("presenting to the T cells a T cell-activating peptide"),

c) incubating the fluid for 6 hours at 37°C in a humidified 5% CO_2 in air incubator ("incubating the fluid to cause release of said IFN-γ"), and

d) overlaying the wells with biotinylated anticytokine antibody for 2 hours; then washing the plates; then treating with a 1/300 dilution of avidin-conjugated alkaline phosphatase for 1 hour; then washing a final time, then visualizing the single cells secreting cytokine by adding a solution of BCIP-NBT to the plates, ("detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells");

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by *in vitro* culture in the presence of the T cell-activating peptide.

It would have been obvious to incorporate Hagiwara's teachings into Miyahara's method. One would have been motivated to use fresh T cells in Miyahara's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Miyahara that were cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Miyahara's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

With regard to claim 45, Miyahara/Hagiwara teach the claimed method/protocol, but both are silent on the embodiment wherein the fluid mixture (T cells and activating peptide) is incubated under non-sterile conditions. The specification does not define exactly what conditions are encompassed by "non-sterile conditions" during incubation. Regardless, it

would have been obvious to one of ordinary skill in the art to forego the benefits of sterile conditions during incubation, step (c) of the method. The method does not require that the results be of any particular quality or accuracy as a result of sterile or non-sterile conditions.

With regard to claims 49-50, the Office does not give patentable weight to the intended uses recited. There is no active monitoring step given the claim language. The Office interprets claims 49 and 50 as essentially saying, "The method as claimed in claim 40, used for performing the monitoring of progress of HIV infection", or "used for performing the monitoring the effect of a vaccine", respectively. Such a limitation does not carry patentable weight, as there are no active steps in the claims that indicate monitoring the progress or effect of an infection or vaccine. One may use the method for whatever purpose desired. If Applicant intends for the monitoring of HIV and vaccine to be active steps, the methods must recite the step in either the claim preamble, or as an active step in the protocol.

13. (*New Rejection*) Claims 40-43 and 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Surcel *et al.* (*Immunology*, 1994, 81:171-176, "Surcel"), in view of Sørensen *et al.* (*Infection and Immunity*, 1995, 63(5):17170-1717, "Sørensen"), and Hagiwara *et al.* (*AIDS Research and Human Retroviruses*, January 20, 1996, 12(2):127-133, "Hagiwara").

Surcel discloses Th1/Th2 profiles in tuberculosis, based on the proliferation and cytokine response of blood lymphocytes to mycobacterial antigens. "Proliferation and cytokine production profiles by blood mononuclear cells in response to in vitro stimulation with mycobacterial antigens were compared in patients with active tuberculosis and in sensitized healthy people", page 171, abstract. Surcel uses the ELIspot assay to measure effector T cells

that produce IFN-γ. Surcel's method uses freshly isolated PBMC from patients with active tuberculosis. The cells are incubated in 96-well plates for 72 hours, in the presence of antigen, before transfer to anti-IFN-γ antibody-coated nitrocellulose-bottomed plates in the presence of a mycobacterial antigen. The cells were then incubated for 20 hours and subsequently enumerated (page 172, second column, last three paragraphs). Surcel is silent on the ESAT-6 mycobacterial antigen.

However, Sørensen discloses the discovery of a low-molecular-mass T-cell antigen secreted by *Mycobacterium tuberculosis*. Sørensen teaches that ESAT-6 is a 6-kDa early secretory antigenic target. Sørensen discloses that native and recombinant ESAT-6 elicited a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis* (abstract).

It would have been obvious to use ESAT-6 as the activating peptide in Surcel's ELIspot method. One would have been motivated to use ESAT-6 because it is a T cell epitope. Surcel's method is aimed at studying the relationships between epitope specificity and T cell function (page 172, first column, first paragraph). One of ordinary skill in the art would have been motivated to use Sørensen's antigen as the activating antigen in order to understand the relationship between the ESAT-6 specificity and T cell function. One would have had a reasonable expectation of success based on Sørensen's disclose that ESAT-6 elicited a high release of IFN-γ from T cells isolated from memory-immune mice challenged with *M. tuberculosis*.

Surcel's measurement of IFN-gamma producing T cells involves incubation of T cells in the presence of a T cell-activating peptide for, what is reasonably deduced from the context of

the protocol, 72 hours (page 172, second column, fourth full paragraph). The incubation of T cells with T cell activating peptide for 72 hours would allow memory T cells to proliferate, thus the measurement of IFN-gamma producing T cells would include both the memory T cells and effector T cells. This measurement of both memory and effector T cells is not the instantly claimed invention's method of measuring only effector T cells. However, Hagiwara teaches that ELIspot results are divergent when studying PBMC that have been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients, the same concept applies to Surcel's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo*. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals (see Hagiwara, page 128). The method of assay in which peptide-specific effector T-cells are enumerated, comprises:

a) providing PBMCs from HIV-infected subjects ("a fluid containing fresh T cells") which have not been cultured *in vitro*, in contact with a 96-well nitrocellulose-backed microtiter plate coated with anticytokine antibodies ("a surface carrying an immobilized antibody to interferon-γ"),

b) stimulating the cells with a 1:100 dilution of phytohemagglutinin ("presenting to the T cells a T cell-activating peptide"),

c) incubating the fluid for 6 hours at 37°C in a humidified 5% CO_2 in air incubator ("incubating the fluid to cause release of said IFN-γ"), and

d) overlaying the wells with biotinylated anticytokine antibody for 2 hours; then washing the plates; then treating with a 1/300 dilution of avidin-conjugated alkaline phosphatase for 1 hour; then washing a final time, then visualizing the single cells secreting cytokine by adding a solution of BCIP-NBT to the plates, ("detecting release IFN-γ bound to said immobilized antibody to enumerate said peptide-specific effector T cells");

wherein incubation is continued for a time to permit IFN-γ release by only those T cells that have been pre-sensitized *in vivo* to the T cell-activating peptide and are capable of immediate effector function without the need to effect division/differentiation by *in vitro* culture in the presence of the T cell-activating peptide.

It would have been obvious to incorporate Hagiwara's teachings into Surcel's method. Surcel's method is intended for measuring effector T cells (active tuberculosis versus sensitized healthy controls, see Surcel's abstract). One would have been motivated to use fresh T cells in Surcel's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Surcel that were cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Surcel's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

With regard to claim 45, Surcel/Hagiwara teach the claimed method/protocol, but both are silent on the embodiment wherein the fluid mixture (T cells and activating peptide) is incubated under non-sterile conditions. The specification does not define exactly what

conditions are encompassed by "non-sterile conditions" during incubation. Regardless, it would have been obvious to one of ordinary skill in the art to forego the benefits of sterile conditions during incubation, step (c) of the method. The method does not require that the results be of any particular quality or accuracy as a result of sterile or non-sterile conditions.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

14. Applicant's arguments regarding the combination of the Miyahara and Hagiwara references have been carefully considered, but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that one of ordinary skill in the art would not have been motivated to combine the teachings of Hagiwara and Miyahara. Applicant argues that the Miyahara reference uses an ELIspot with T cells that have been cultured *in vitro*, as opposed to Hagiwara's fresh T cells that have not been cultured *in vitro*. Applicant asserts that Miyahara teaches precisely what Hagiwara advises against.
  - In response to Applicant's argument, the Office agrees with Applicant's characterization of the teachings of Miyahara and Hagiwara. In fact, the Office's motivation for modifying the method of Miyahara with Hagiwara stems from Hagiwara's disclosure that ELIspot results are divergent when studying PBMCs that have been cultured and stimulated *in vitro*. While Hagiwara's disclosure is directed to cytokine production in HIV patients,

the same concept applies to Miyahara's ELIspot. Hagiwara teaches that since the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed, inconsistent results from such studies are not unexpected (page 131, first column). Hagiwara chose an alternative strategy, which was to study cells actively secreting cytokines *in vivo*. Hagiwara's technique monitored the pattern of cytokines produced by cells participating in ongoing immune responses in HIV-infected individuals.

- It would have been obvious to incorporate Hagiwara's teachings into Miyahara's method. One would have been motivated to use fresh T cells in Miyahara's method in view of Hagiwara's teachings about how the type and amount of cytokine produced *in vitro* can be altered by the culture conditions employed and that inconsistent results from such studies are not unexpected. Given this teaching, one of ordinary skill in the art would have been motivated to reduce inconsistent results by using fresh T cells, rather than the cells used by Miyahara that were cultured *in vitro* prior to the ELIspot assay. One would have had a reasonable expectation of success that the use of fresh T cells in Miyahara's method would have worked because Hagiwara's method uses fresh T cells in an ELIspot assay.

- Applicant also argues that if the *in vitro* response of T cells to specific peptides were to be examined, the peptides must be placed in proximity to T cells for some finite time period. Applicant argues that one would not have combined Hagiwara's teachings with Miyahara's method because Hagiwara uses a PHA mitogen. The

mitogen binds via a different mechanism and would be expected to stimulate the cells with different characteristics and kinetics compared with the more specific responses triggered via the T cell receptor. Applicant asserts that at the time of Hagiwara's disclosure, 1996, long *in vitro* incubation times were though to be required to obtain T cell responses to specific peptides derived form cognate antigen.

- In response to Applicant's arguments, the combination of references results in Miyahara's ELIspot,, as disclosed, with the modification/incorporation of Hagiwara's suggestion to use fresh T cells that are not incubated *in vitro* to measure effector T cell function, and a 6 hour incubation time for activation of effector T cells (Hagiwara's method, page 128). Regardless of what is used to activate the effector T cells, one would have successfully used Miyahara's antigen to activate the effector T cells. Since PHA is known to activate T cells, and Miyahara's antigen activates T cells, the mechanism of how the T cells are activated is irrelevant. All that is required from Miyahara and Hagiwara is that the T cells be activated so that IFN-gamma is secreted.

- Applicant further argues that the validity of the ELIspot for quantitative use is argued on the ground that the ELIspot generates very similar results to those obtained with standard Limiting Dilution Analysis (LDA). Applicant notes that LDA makes no distinction between memory progeny T cells and effector T cells.

  - In response to Applicant's argument, the comparison of the ELIspot and LDA is irrelevant in view of Hagiwara's teachings. Hagiwara sets forth the

problem to be solved by modifying the ELIspot assay for measurement of effector T cells. Thus, the results of ELIspot and LDA with regard to measuring memory T cells in addition to effector T cells would be overcome when incorporating Hagiwara's teachings into the ELIspot of Miyahara.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

15. No claim is allowed. In view of the new grounds of rejection, this Office action is made non-final.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Stacy B. Chen 4/10/07

STACY B. CHEN
PRIMARY EXAMINER